REMARKS

Claims 25-41 and 44-55 are pending. Claim 27 has been amended. No new matter is presented by virtue of the within amendments; support therefore can be found throughout the specification and original claims.

Claim Objections

Claim 27 was objected to under 37 CFR §1.75(c) as allegedly failing to further limit the subject matter of a previous claim. Claim 27 has been amended to recite that the preparation contains "at least one further substantially neutral isotonising agent". With that amendment, the subject matter of claim 27 clearly recites an additional feature beyond those recited in claim 25 and consequently further limits the subject matter of claim 25. Reconsideration and withdrawal of the objection are requested.

Claim Rejections

For the sake of brevity, the rejections under 35 USC §103(a) are summarized below and addressed in combination.

Claims 25-26, 29-30, 35-41 and 44-55 stand rejected under 35 U.S.C. §103(a) over Malvolti (WO 03/004005) in view of Hughes et al. (*The Lancet*, Vol. 361, No. 9375, pages 2114-2117, 2003).

Claims 25-26, 29-30, 36-41 and 44-55 stand rejected under 35 U.S.C. §103(a) over Montgomery (U.S. 6,083,922) in view of Hughes et al.

Claims 27-28 and 31-33 stand rejected under 35 U.S.C. §103(a) over Malvolti et al. in view of Hughes et al., as applied to claims 25-26, 29-30, 35-41 and 44-55, and further in view of Wiedmann et al. (U.S. 5,747,001).

Claim 34 stands rejected under 35 U.S.C. §103(a) over Malvolti et al. in view of Hughes et al., as applied to claims 25-26, 29-30, 35-41 and 44-55, and further in view of Azria et al. (U.S. 5,759,565).

Each of the rejections is traversed. The cited documents, even in the stated combinations, fail to teach or suggest the features of the present invention in any manner sufficient to sustain any one of the rejections.

The Office Action alleges that Malvoti and Montgomery disclose the claimed invention, except for the addition of a magnesium or calcium salt. Hughes is added to each of Malvoti and Montgomery for its teaching relative to the effect of isotonic magnesium administered adjunct to nebulized salbutamol. Hughes indicates that the magnesium led to an enhanced bronchodilator response in severe asthma (in comparison to use of an isotonic saline solution).

The Examiner takes the position that one skilled in the art would have combined these elements, thus arriving at the present invention in an obvious manner.

The Examiner expressly acknowledges the deficiencies of Malvoti and Montgomery, but considers that the use of magnesium and calcium salts for inhalation solutions was logical in view of Hughes et al.

As for the remaining rejections, Wiedmann is added and applied for its disclosure of formulations with a surface modifier for nebulization. Likewise, Azria is added and relied on for its disclosure of viscosity and tonicity requirements.

Hughes et al. is applied in each of the §103(a) rejections for its teaching relative to the effect of isotonic magnesium administered adjunct to nebulized salbutamol. Applicant submits, however, that Hughes et al. would not have suitably been combined with the other applied references as proposed. Even if it were, the combinations are still deficient and cannot sustain the rejections.

For instance, Hughes et al. states that an isotonic magnesium solution can be used as an adjuvant for inhaled salbutamol. Salbutamol is a **β_2 mimetic**, which induces **relaxation of the airway muscles** after interaction with the β_2 receptors of these airway muscles. As this relaxation of airway muscles results in **bronchodilation**, the drug is used to relieve the **bronchoconstriction** during asthma attacks. On the other hand, it is generally known that a lack of magnesium can induce undesired muscle contractions. This means that magnesium supplementation could avoid these contractions. It is therefore not unexpected that magnesium has an adjuvant effect when it is combined with salbutamol in inhalation solutions.

However, the tobramycin formulation of the present invention is not intended to relieve **bronchoconstrictions**, but rather it is for the treatment of **bacterial infections**. When formulating a drug for treatment of bacterial infections, one skilled in the art would not rely on prior art relating to bronchodilation.

Indeed, the objective of the present invention is fundamentally different from that of the formulations described by Hughes. In short, Hughes only uses magnesium for its bronchodilating effect; tobramycin is not a drug used for bronchodilation. Therefore, one skilled in the art would not look to prior art describing bronchodilation for preparing a tobramycin formulation, especially not in concentrations far below the isotonic concentrations (as in the present invention).

Additionally, the present inventors unexpectedly discovered that the current formulation has a higher affinity for sputum than a formulation not containing the magnesium and calcium salts (see the Applicant's remarks in response to the previous Office Action). This is definitely advantageous for the antibacterial efficacy of the present formulation, but is not related to the effects of magnesium described in the specification (i.e. bronchodilation). Furthermore, the solution used by Hughes et al. was an **isotonic** solution, whereas the concentration of the magnesium and calcium salts in the claimed formulation is far lower.

More details on tobramycin and its use in, for example, cystic fibrosis patients can be found in paragraphs [0002] to [0010] of the specification. The reference to Hughes et al. in the specification was offered only as support for the (harmless) applicability of magnesium salts in inhalation products, for whatever indication.

It is possible that the effects described by Hughes et al. might also occur when administering magnesium salts in combination with tobramycin instead of with salbutamol (although it is doubtful that the effect described with the isotonic magnesium concentration will also occur when using a far lower concentration – for bronchodilation, the concentration of magnesium salts must be about 100 fold higher). These effects might even be advantageous for tobramycin aerosol delivery. However, the advantageous and unexpected effect of a combination of magnesium and calcium salts in the claimed tobramycin formulation is unrelated to the previously described bronchodilation effects of magnesium salts.

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." Id. Four factual inquiries must be made: first, a determination of the scope and contents of the prior art; second, a determination of the differences between the prior art and the claims in issue; third, a determination of level of ordinary skill in the pertinent art; and fourth, an evaluation of evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant

combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

The Office Action expressly acknowledges that Malvoti and Montgomery each lack disclosure on the addition of a magnesium or calcium salt. The Examiner relies on Hughes et al. for that component. However, for at least the reasons set forth above, there is no reason to combine Hughes et al. with the other cited references. There is no suggestion or motivation to combine the references as proposed; nor is there any reasonable expectation of success. In any case, Hughes et al. still fails to remedy the deficiencies of the primary references. Consequently, the rejections should be withdrawn.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for immediate allowance.

FEE AUTHORIZATION

While no fees are believed to be due, the Commissioner is authorized to charge any fees associated with this submission to our Deposit Account, No. 04-1105, Reference 65177(45107). Any overpayment should be credited to said Deposit Account.

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Respectfully submitted,

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